Initial Experience With Crotalidae Polyvalent Immune Fab (Ovine) Antivenom in the Treatment of Copperhead Snakebite

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Study objective: Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) effectively treats patients bitten by rattlesnakes. The copperhead snake (*Agkistrodon contortrix*) caused 37% of venomous snakebites reported to US poison centers in 2001 and is the major envenomating reptile in the southeastern United States. FabAV has not been tested in human beings envenomated by copperhead snakes.

Methods: In this preliminary study, we performed a retrospective chart review of all copperhead snake envenomations reported to the Carolinas Poison Center that were treated with FabAV. Progression of limb swelling, coagulopathy, and hemodynamic status before and after FabAV administration, adverse effects of FabAV therapy, and recurrence phenomena were recorded.

Results: Of approximately 400 copperhead envenomation cases reported to the poison center during the study period, 32 received FabAV and were included. Most patients had moderate envenomation. The median time to FabAV administration was 4.0 hours. The median time to achieve initial control was 1.0 hour, with a median dose of 4 vials of FabAV. A rapid initial response, defined as cessation of the progression of local tissue injury within 4 hours of FabAV administration, occurred in 28 cases (88%; 95% confidence interval [CI] 76% to 99%). Four cases (13%; 95% CI 1% to 24%) were considered treatment failures. Recurrent swelling occurred in 6 cases (19%; 95% CI 5% to 32%). The incidence of recurrent swelling was not reduced by administration of repeated doses of antivenom on a planned schedule. One patient developed late-onset coagulopathy. One minor allergic reaction was observed.

Conclusion: In this select group of patients bitten by copperhead snakes, local tissue effects of envenomation halted promptly after FabAV treatment in most cases. Treatment failures occurred, and recurrence of swelling and defibrination syndrome was sometimes problematic. Time to return to work and long-term limb function were not assessed. A controlled trial with long-term follow-up is needed to define the role of FabAV treatment for copperhead envenomation.

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Capsule Summary

What is already known on this topic

Published experience with the use of Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) fragments for copperhead envenomation is limited.

What question this study addressed

This uncontrolled review of experience using FabAV fragments in 32 selected copperhead snakebite victims sought to determine whether local tissue injury could be arrested quickly and permanently with doses similar to those used for rattlesnakes.

What this study adds to our knowledge

FabAV fragments appear to stop the swelling associated with copperhead envenomation in most cases, but it will recur in some cases. No statement can be made about an intermediate- or long-term outcome benefit (eg, time to recovery or return to work, tissue loss, function). FabAV use was safe in this group.

How this might change clinical practice

In selected cases of copperhead envenomation at increased risk for significant tissue injury, FabAV fragments may be considered to reduce ultimate swelling and possibly reduce tissue injury. Its use will be expensive.

INTRODUCTION

Background

One of the most common envenomating reptiles in the United States is the copperhead snake (*Agkistrodon contortrix*). A new antivenom is replacing Antivenin (Crotalidae) polyvalent (equine) as the standard pit viper antivenom in the United States. It is not known whether the new antivenom, Crotalidae polyvalent immune Fab (ovine) (CroFab; FabAV) is beneficial for treating copperhead snakebite.

Importance

In 2001, 769 copperhead envenomations were reported to US poison centers, representing 37% of all venomous snakebites in which the species was known.[1] In parts of the Southeast and Texas, this proportion increases to 56% to 88% of all snakebites (Carolinas Poison Center, internal data, 2003).[2-4] Many more cases undoubtedly occur but are not reported to poison centers. Published reports demonstrate that these injuries are often serious: 43% to 100% of patients are hospitalized, with 6% to 27% of patients admitted to critical care units.[3,5-7] Although extremely rare, deaths caused by copperhead envenomation have been reported.[1] Because of the risk of allergic reaction to equine-derived antivenom, only 0% to 10% of patients in previously published case series received antivenom.[2,6-8] However, local tissue injury was often significant. In one study with follow-up data for 18 patients, one of whom received equine-derived antivenom, the median duration until return to full duties at work was 44 days.[7]

In October 2000, the US Food and Drug Administration (FDA) approved FabAV for "treatment of minimal and moderate North American Crotalidae envenomation." Although the FDA indication includes victims of all types of crotaline snakes, including copperheads, this approval was based entirely on experience with rattlesnake victims.[9-11] Copperhead venom is not used in the preparation of FabAV, and victims of copperhead snakebite were excluded from clinical trials.[10,11] The only data evaluating whether FabAV neutralizes copperhead venom are from a mouse model,[12] and the only published experience with use of FabAV in human copperhead envenomations consists of 2 case reports.[13,14]

Goals of This Investigation

No previous study has examined whether FabAV provides clinical benefit to copperhead snakebite victims. Unfortunately, a nationwide antivenom shortage during the 2001 and 2002 snakebite seasons made a controlled trial impossible. Therefore, to gather initial data about the safety and efficacy of FabAV in copperhead snakebite, we performed a structured chart review.

MATERIALS AND METHODS

Theoretical Model of the Problem

Copperhead snakebite can cause pain, swelling, local tissue injury, coagulopathy, thrombocytopenia, hypotension, bleeding, and loss of limb function. Antivenom binds and inactivates venom components, reducing or eliminating these effects.

Study Design and Setting

The study design consisted of a consecutive sample case series.

This study was conducted through the Carolinas Poison Center, the only designated poison center in North Carolina. Southern copperhead snakes (*A c. contortrix*) are responsible for 85% of venomous snakebites in North Carolina and, in much of the state, are the only indigenous venomous reptile. This study was approved by the institutional review board of Carolinas HealthCare System.

Selection of Participants

All cases of human snake envenomation reported to the Carolinas Poison Center from October 2000 until October 2002 were reviewed. Patients were included if the snake was identified as *A contortrix*, FabAV was administered, and local tissue injury was progressing at initial FabAV administration.

Snake species identification was made by a variety of methods, as shown in Table 1. A herpetologist identified North Carolina counties in which copperhead snakes are the only indigenous venomous snake. Patients bitten outdoors in these counties were considered to have been bitten by copperheads. Otherwise, snakes were visually identified as copperheads by emergency medical services (EMS) or hospital personnel, the patient or family, or, in the case of captive snakes, the snake owner.

Measurements

Poison center and patient treatment records were reviewed to record pain, swelling, hemodynamic status, evidence of coagulopathy, and evidence of compartment syndrome before and after FabAV administration. Recurrence phenomena and adverse effects of FabAV were also recorded. Because the primary clinical effect of copperhead envenomation is usually severe pain and swelling in the envenomated limb, we collected data about the progression of swelling before and after FabAV administration. The retrospective nature of the study, the subjective nature of pain severity recording, and the concomitant administration of narcotic analgesics made reporting of pain severity unreliable. We recorded coagulation laboratory studies (prothrombin time, partial prothrombin time, and fibrinogen), platelet count, and the occurrence of clinical bleeding or compartment syndrome. Information on treatment included time from envenomation to FabAV administration, FabAV dose, complications of FabAV therapy, surgical intervention, recurrence phenomena (any worsening of local tissue, hematologic, or systemic effects after stabilization), and length of hospitalization.

Table 1.
Patient characteristics.

Characteristic	No. of Patients (%)
Sex, male	27 (84)
Age, y	
3–17	8 (25)
18–34	1 (3)
35–64	16 (50)
≥65	7 (22)
Bite location	
Upper extremity	24 (75)
Lower extremity	8 (25)
Snake species identification	
Geographic*	14 (44)
Private collection	1 (3)
Identification by EMS or ED personnel	5 (16)
Identification by patient or family only†	12 (38)
Severity[9]	
Mild	5 (16)
Moderate	25 (78)
Severe	2 (6)
Treated in person by author	
Yes	11 (34)
No (poison center contact only)	21 (66)

*Although rattlesnakes (*Crotalus* sp), pygmy rattlesnakes (*Sistrurus* sp), water moccasins (*A piscivorus*), and coral snakes (*Micrurus fulvius*; Elapidae) can be found in parts of the North Carolina mountains and coastal plain, the only indigenous poisonous reptile in much of central North Carolina is *A contortrix*. Patients with a history of envenomation outdoors in this region were considered to have been bitten by a copperhead.
†Reevaluation of data with these cases excluded does not change the findings of this article.

Data Collection and Processing

Data were abstracted by 1 of 2 authors (EJL or WPK) into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). In many cases, ED and hospital records were also available. When data were unclear or missing from the record, an author contacted the treating physician. Clinical observations and poison center call backs, although frequent, were not made on a set schedule.

Outcome Measures

The primary study outcome was time from FabAV administration until cessation of progression of limb swelling. Secondary outcomes examined included recurrent swelling, initial or delayed coagulopathy and thrombocytopenia, pain, hypotension, and adverse reactions to FabAV. Because progression of local tissue injury was often gradual and observations were typically spaced 2 to 4 hours apart, in some cases there was uncertainty about the exact time swelling either stopped progressing or resumed. These periods of uncertainty are depicted graphically on the Figure as error bars. The midpoint of any period of uncertainty was used in calculations.

Overall clinical severity was classified as mild, moderate, or severe by using standard criteria.[9]

As in previous studies, initial control of envenomation was defined as cessation of progression of local tissue injury and absence of hypotension or systemic bleeding.[9,10] A rapid initial response to antivenom was defined as initial control achieved within 4 hours of com-

pletion of the first dose of FabAV. Recurrence phenomena were classified as early if they developed within 6 hours of initial control and late if they developed after 6 hours.

A treatment failure was defined as either failure to achieve initial control within 12 hours of the first dose of FabAV or progression in severity classification (from mild to either moderate or severe, or from moderate to severe) at any time after FabAV administration.

Data Presentation

Because this is an observational study in which all patients received FabAV, in most cases observations are presented as proportions with 95% confidence intervals (CIs). When appropriate, Fisher's exact test was used for comparison between small groups.

RESULTS

Characteristics of Study Subjects

Approximately 400 cases of copperhead snake envenomation were reported to the poison center during the study period, and 32 (8%) patients were treated with FabAV. Demographic characteristics for these 32 patients are presented in Table 1. All of these patients were admitted to the hospital, with a median length of stay of 40 hours (range 7 hours to 8 days). Follow-up data were not consistently available after hospital discharge.

Most patients were not systemically ill. No patient developed hypotension or respiratory failure, required amputation, or died. On presentation, 3 patients had minimal protime elevations (international normalized ratio 1.4 to 1.5; normal 0.9 to 1.2), 1 patient had mild hypofibrinogenemia (157 mg/dL; normal 200 to 400 mg/dL), and 4 patients had mild thrombocytopenia (range 122,000 to 141,000/μL; normal 150,000 to 400,000/μL). Two other patients had coagulopathy at baseline from preexisting medical conditions. One patient, described later in this section, developed severe defibrination late in his clinical course. No patient developed systemic bleeding.

The median time from envenomation until initial FabAV administration was 4.0 hours (range 1.5 to 39 hours). In 8 cases (25%), administration was delayed

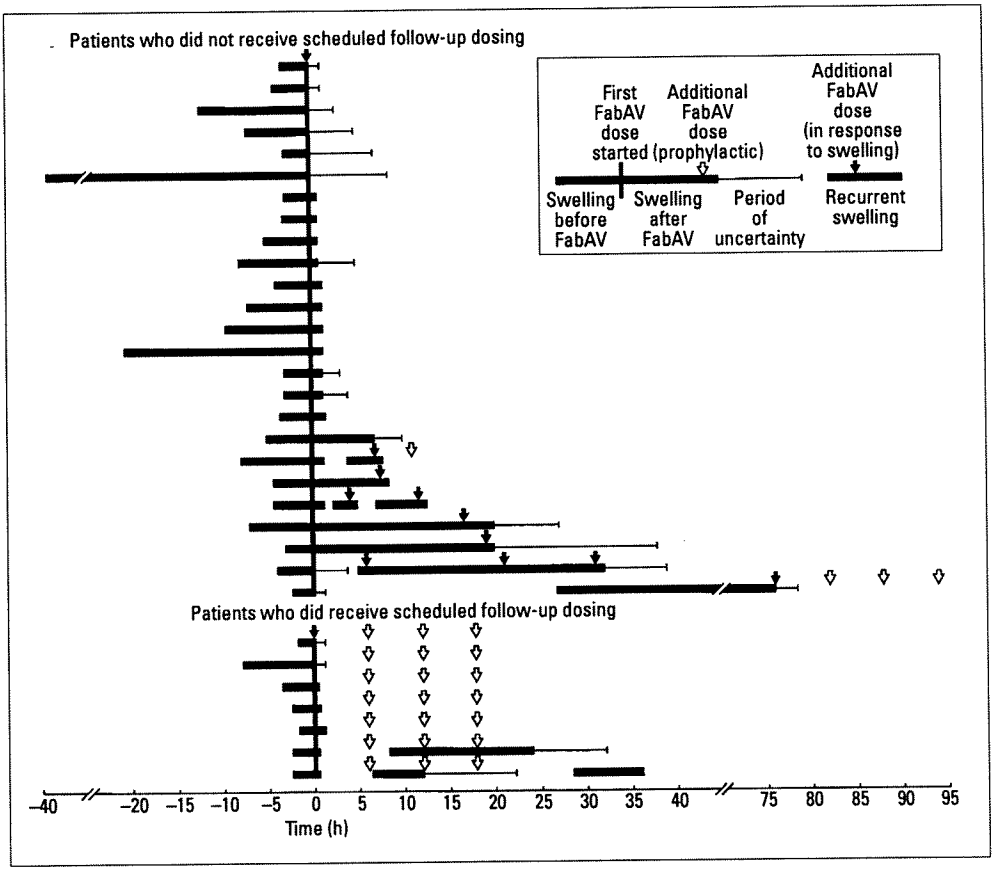

Figure.
Time course of swelling and FabAV therapy.

because sufficient FabAV was not available in the treating institution.

Main Results

The median time to achieve initial control was 1.0 hour (range 0.25 to 23.75 hours). A rapid initial response to FabAV was achieved in 28 of the 32 cases (88%; 95% CI 76% to 99%). The doses used to achieve initial control are presented in Table 2. Although we did not solicit these data, caregivers spontaneously reported that swelling or pain improved during FabAV infusion in 12 cases.

FabAV treatment appears to have prevented fasciotomy in one patient. A 12-year-old boy was bitten in the hand. An orthopedic surgeon diagnosed compartment syndrome 4 hours after envenomation. Compartment pressures were not measured. While the surgical team was assembling, the patient received 4 vials of FabAV. Swelling improved after FabAV infusion, and the planned fasciotomy was cancelled. The patient was discharged with good hand function.

Four cases met the criteria for treatment failure. In 2 cases, initial control was not achieved within 12 hours of FabAV therapy. In the first case, local tissue effects progressed despite 24 vials of FabAV being given during 31 hours. In this case, the snake was identified only by the patient. In the other case, the patient received 4 vials of FabAV 3 hours after a hand envenomation that occurred in a portion of the state with no venomous snakes other than copperheads. Swelling continued to progress but never extended beyond the wrist. A second 4-vial dose of FabAV was given 17 hours later, with prompt improvement.

The other 2 treatment failures involved patients whose severity classification progressed after FabAV therapy. Both were bitten on the hand. In the first case, the patient was bitten in a locale with no pit vipers other than copperheads. Swelling and ecchymosis halted at the elbow (moderate severity), briefly regressed after 4 vials of FabAV had been administered, and then resumed 2 hours later, ultimately involving the entire upper extremity, ipsilateral torso, lower extremity, and scrotum (severe envenomation). Eight additional vials of FabAV were given, with no discernible effect. Despite this severe progression, the patient returned to full duties at a steel mill within 2 weeks and experienced no permanent sequelae. The other patient had mild (hand only) swelling that stabilized immediately after he received 4 vials of FabAV. Snake species identification occurred in the ED. Initial protime, partial prothrombin time, and platelet measurements were normal. Recurrent swelling began 24 hours later. By 36 hours after envenomation, his arm was swollen above the elbow (moderate severity), and severe coagulopathy was present (fibrinogen undetectable, prothrombin time >100 seconds). Fresh frozen plasma and 4 additional vials of FabAV were administered 78 hours after envenomation, followed by maintenance doses of FabAV given 6, 12, and 18 hours later. Thrombocytopenia and bleeding never developed. Swelling improved, and coagulation parameters normalized promptly with retreatment.

Recurrent local tissue effects developed in 6 of the 32 patients (19%; 95% CI 5% to 32%). Early recurrent swelling developed in 4 of these 32 cases (13%; 95% CI 1% to 24%) but was mild and easily controlled with repeated FabAV dosing in 2 cases and mild but poorly responsive to antivenom in a third. The fourth case, with severe recurrent edema refractory to retreatment, was described previously. Two of the 28 patients who did not have recurrent swelling within 6 hours of initial treatment developed late recurrent swelling (7%; 95% CI 0.9% to 24%). One was mild and did not require intervention. The severe case, involving delayed defibrination syndrome, was described previously.

The manufacturer of FabAV recommends administering maintenance doses of antivenom 6, 12, and 18 hours after initial control is achieved to reduce the risk of recurrent swelling.[11] Initial control was achieved and maintained for 6 hours in 27 patients. Seven patients received scheduled maintenance FabAV doses, whereas the remainder received additional antivenom only as needed. These groups did not differ in age, bite location, or severity of envenomation. Late recurrent swelling developed in 2 patients of the 7 patients who received maintenance therapy (29%; 95% CI 4% to 71%) and in 1 patient of the 20 patients who did not (5%; 95% CI 0.1%

Table 2.
FabAV dose used for initial control.

FabAV Dose	No. of Patients (%)
No. of vials	
4	23 (72)
5	1 (3)
6	4 (13)
8	1 (3)
Record unclear	1 (3)
Initial control not achieved within 12 h	2 (6)*

*Four and 24 vials; see text.

to 25%). This difference in frequency was not statistically significant (P=.156, Fisher's exact test), but this study lacked the power to detect a difference if the baseline incidence is low.

The only possible acute allergic reaction involved a single patient who developed "hot flashes" and tachycardia during FabAV infusion (incidence: 3%; 95% CI 0.1% to 16%). Wheezing, swelling, and urticaria were not observed. Symptoms resolved with diphenhydramine and slowed infusion rate. FabAV administration was completed without further difficulty.

Limited data are available about serum sickness. Follow-up information at least 21 days after FabAV administration are available for 6 patients, 1 of whom (17%; 95% CI 0.4% to 64%) developed signs of serum sickness. This patient, who received 10 vials of FabAV (4 as treatment and 6 as maintenance), developed thrombocytopenia (platelet count 89,000/μL), fever (39.8°C [103.6°F]), myalgias, and rash 14 days after envenomation. His condition resolved with steroid therapy.

LIMITATIONS

As with any retrospective case series, this report has limitations. This was a select group, representing only 8% of copperhead victims. Although made in consultation with a clinical toxicologist, the selection of patients for FabAV therapy was based on varying criteria. Patients receiving FabAV were, in general, more severely affected than those treated with supportive care only. We could not locate an appropriate comparison group of patients with similar severity, either in our internal database or in others' case series. Although this report may provide useful data about the typical clinical course of FabAV-treated patients, it cannot be used to compare results with FabAV to results with supportive care alone. Some patients might have achieved similar outcomes without antivenom, and results may not be generalizable to the entire population of copperhead victims.

This study did not assess whether FabAV prevents long-term disability. Chronic limb dysfunction has been shown in copperhead and rattlesnake victims.[7,15] Whether antivenom reduces this risk is an important question requiring a randomized trial with extended follow-up.

DISCUSSION

To our knowledge, no previously published report analyzes the response to antivenom therapy in human copperhead victims. Copperhead snakebite is a common clinical problem, with at least 700 cases occurring annually. Although copperhead snakebite is almost never lethal, short-term and long-term clinical effects are often significant.[7] Primarily because of concerns about the safety of equine-derived antivenom therapy, 89% to 100% of patients in published case series did not receive antivenom.[2,6-8,16] In our experience during the first 2 years of ovine FabAV availability, 92% of patients were still treated with supportive care only. Specific therapy is certainly desirable.

In this preliminary study, most patients had a dramatic clinical response to FabAV therapy. Local tissue effects typically stabilized within 1 hour of treatment. No safety problems were detected. However, clinical failure occurred in 13% of the patients, and recurrent local tissue effects occurred in 19% of the patients.

Contrary to experience in rattlesnake patients, additional FabAV given 6, 12, and 18 hours after initial control did not reduce the incidence of recurrent swelling in this series of copperhead victims,[10] which may be because the incidence of late recurrent swelling in copperhead patients treated without maintenance FabAV was only 5%, compared with 18% to 50% in rattlesnake cases.[9,10] It may be possible to save considerable cost by avoiding maintenance FabAV dosing therapy in copperhead patients and treating recurrent venom effects only if they occur.

Although no published research has evaluated its effectiveness, CroFab has been approved by the FDA and is being used for copperhead envenomation. Although safety concerns are relatively minor, economic factors may be important in the decision to treat otherwise stable patients with FabAV. Four vials of FabAV cost the hospital pharmacy approximately $3,360, and recommended maintenance therapy adds $5,040 to this cost. Patient charges may be higher, and hospitals bear the burden of care to the uninsured.

In Retrospect

With the introduction of FabAV in the United States, the decision about whether to treat a snakebite victim who does not have life- or limb-threatening injury has become a cost-benefit rather than a risk-benefit calculation. Although the data in this report suggest that most patients who receive FabAV will have excellent short-term outcomes, it is impossible to determine whether the benefit is lasting. The cost of FabAV may be hard to justify unless it leads to shortened hospitalization or reduced long-term disability. Further research to determine the magnitude and duration of benefit is needed.

In summary, in this select group of patients bitten by copperhead snakes, progression of swelling halted promptly after FabAV therapy in most patients. Treatment failures and recurrent effects of envenomation occurred. Time to return to work and long-term limb function were not assessed. Further research is needed to determine whether short- and long-term outcomes are better than those obtained with supportive care alone.

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